Neutrophil: Lymphocyte Ratio and Mean Platelet Volume in Patients with Gout

Gut Hastalığında Nötrofil/Lenfosit Oranı ve Ortalama Trombosit Hacmi

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Özet

Amaç: Gut artmış ürik asit konsantrasyonu ile birlikte monosodyum ürat (MSU) kristallerine karşı oluşan inflamatuar yanıtın yol açtığı klinik bir sendromdur. Gut hastalığında inflamatuar yanıtın oluşmasında nötrofiller önemlidir ve nötrofil aktivasyonu lokal olarak üretilen sitokinlere bağlıdır. Ortalama trombosit hacmi (MPV) ve nötrofil lenfosit oranı (NLR) bazı hastalıklarda inflamatuar belirteç olarak değerlendirilmiş ve prognostik öneme sahip olabileceği bildirilmiştir. Bildiğimiz kadarıyla literatürde gut hastalığında MPV ve/veya N/L oranının değerlendirildiği bir çalışma yoktur. Biz bu retrospektif çalışmamızda gut hastalığında inflamasyonun belirlenmesinde MPV ve NLR' nin rolünü araştırdık. Gereç ve Yöntem: Retrospektif olarak dizayn edilmiş olan bu çalışmaya gut hastalarının dosyaları taranarak çalışmaya dahil edilme kriterlerini karşılayan toplam 106 (91 erkek, 15 kadın) gut hastası ve yaş-cinsiyet eşleştirmeli 148 (128 erkek, 20 kadın) sağlıklı kontrol grubu alındı. Hasta grubunun atak dönemi (Grup I) ve ataksız dönemi (grup II) laboratuvar verileri toplandı. Bulgular: Gut hasta grubu yaş ortalaması 59.46±12.93 yıl, sağlıklı kontrol grubu yaş ortalaması 59±11.33 yıl idi. Her iki grup yaş ve cinsiyet açısından benzerdi. İlk atak yaşı 52±12.77 yıl, ilk iki atak arası süre 6±5.52 ay idi. Hastaların 9'unda (%8.5) tofüs, 17'sinde (%16) gut aile öyküsü vardı. MPV her üç grupta da benzerdi. CRP ve eritrosit sedimentasyon hızı, atak dönem gut hasta grubunda ataksız dönem gut hasta grubuna göre istatistiksel anlamlı yüksek saptandı. N/L oranı her üç grupta da istatistiksel olarak anlamlı farklılık gösteriyordu. Tofüs varlığına göre hastalar sınıflandırıldığında ise her iki grupta da MPV ve N/L oranının benzer olduğu görüldü. Tartışma: N/L oranı hem atak hem ataksız dönem gut hastalarında sağlıklı kontrol grubuna göre artmıştı. Bu çalışma gut hastalarının kronik inflamasyona maruz kaldığını göstermektedir. Bu nedenle N / L oranı gut hastalığında inflamasyonun gösterilmesinde basit, ucuz ve kullanışlı tanısal belirteç olabilir.

Anahtar Kelimeler

Gut; Nötrofillenfositoranı; Ortalama Trombosit Hacmi

Abstract

Aim: Gout is a clinical syndrome with increased uric acid concentration, which is caused by inflammatory response against monosodium urate (MSU) crystals. In gout, neutrophils are involved in inflammatory response and neutrophil activation is dependent on local cytokine production. Mean platelet volume (MPV) and neutrophillymphocyte ratio (NLR) are considered as inflammatory markers in several diseases and it is reported that they may have prognostic significance. Inthe current literature, there is no study evaluating MPV and NLR in gout. In this retrospective study, we investigated the role of MPV and NLR in determining inflammation in gout disease. Material and Method: In this retrospective study, 106 patients with gout (91 men and 15 women) meeting the inclusion criteria based on patient records and 148 age- and sex-matched healthy controls (128 men and 20 women) were included. Laboratory data during attacks (group I) and intercritical period (group II) were collected for the patient group. Results: Mean age was 59.46±12.93 years in the patient group and 59.00±11.33 years in the control group. Age at first attack was 52.00±12.77 years and mean time interval between first 2 attacks was 6.00±5.52 months. There was tophus in 9 patients (8.5%) and family history of gout in 17 patients (16.0%). Compared to groupII (intercritical period) and the control, no significant difference in MPV levels was found in groupI (during attack). MPV was similar among the three groups. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were found to be significantly higher in group I compared to group II. There was significant difference in NLR among three groups. When classified according to the presence of tophus, it was seen that MPV and NLR were similar in both groups. Discussion: The finding of increased NLR during attacks and intercritical period show that patients with gout are subjected to chronic inflammation. Thus, NLR can be a simple, inexpensive, and useful diagnostic marker in gout. Studies comparing cytokine levels with NLR will be helpful in elucidating this topic.

Keywords

Gout; Mean Platelet Volume; Neutrophil Lymphocyte Ratio

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Introduction

Gout, which results from increased serum urate concentration, is a disorder characterized by acute arthritis attacks and deposition of monosodium urate (MSU) crystals in tissues. It dates back at least to the time of Hippocrates, who first described the disorder.The acute form generally appears as a self-limiting, severe inflammatory arthritis that progresses with recurrences. In chronic form, aggregates formed by MSU crystals (tophus) primarily accumulate within and around the joint. Gout arthritis affecting 1-2% of adults is the most frequent cause of inflammatory arthritis among men [1,2].

Synovial cells, monocytes, and neutrophils play a role in the precipitation of gout arthritis. The majority of responses observed in clinical presentation are mediated by neutrophils. In an acute gout attack, cytokines such as IL-1, IL-6, and tumor necrosis factors alpha (TNF-α) are produced in excessive amounts that are sufficient to pass systemic circulation and to induce acute phase response [3].

In a complete blood count, platelet size is expressed as mean platelet volume (MPV). MPV is indirectly linked to platelet activity. Larger platelets are more active than smaller ones in terms of metabolic and enzymatic activity [4-9]. Neutrophillymphocyte ratio (NLR) is a marker that can be estimated by using leukocyte subtypes from the complete blood count. Moreover, it has been reported that NLR may have prognostic value in some diseases [7,8].In the current literature, there is no study evaluating MPV and NLR together in gout. In this retrospective study, we investigated the role of MPV and NLR in the determining disease activity in gout disease.

Material and Method

Patients and method

The patients who were followed with a diagnosis of gout were assessed according to the inclusion criteria (August 2014-April 2015). Overall, 106 patients with gout (91 men and 15 women) meeting the criteria were included in the study based on the clinical files of patients. As controls, 148 age- and sex-matched healthy individuals (128 men and 20 women) were included.

Inclusion criteria:

- Gout diagnosis based on diagnostic criteria suggested by American College of Rheumatology (ACR)
- No known coronary artery disease
- No medication known to affect serum uric acid levels such as aspirin, diuretics etc.
- No history of smoking and/or alcohol consumption
- No steroid and/or immunosuppressive agent use at the time of blood sampling based on measurements of laboratory parameters including complete blood count, erythrocyte sedimentation rate, and C-reactive protein
- No infection at the time of blood sampling based on measurements of laboratory parameters includingcomplete blood count, erythrocyte sedimentation rate, and C-reactive protein

The laboratory data during attack (group I) and intercritical period (group II) were collected for 106 patients with gout who met the inclusion criteria. The patients with gout were classified into subgroups according to the presence of tophus. In all patients and controls, demographic data, disease characteristics, and laboratory data were recorded in a data sheet developed by researchers. In addition, MPV, NLR, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) values were recorded in the data sheet. Complete blood count was performed by laser and impedance method with a CellDyn 3700 analyzer while CRP was determined by the immunoturbidimetric method with an ArchiTect 4100 analyzer. ESR was determined using biomedical systems compatible with the Westergreen method. The study was approved by the Local Ethics Committee. All includedpatients gave informed consent.

Statistical analysis

Definitive data are presented as mean ± standard deviation, frequency, and percent. Student's t test or Mann-Whitney U test were used to assess difference in numerical values between study groups. Kruskal-Wallis test was used to assess difference in multiple comparisons. In case of significant difference, pairwise comparisons were performed using Mann-Whitney U test with Bonferroni-DUM procedure (alpha=0.017). Spearman's rank correlation coefficient was used to assess associations between numerical values. All analyses were performed using SPSS for Windows version 13.0 (SPSS Inc., Chicago, Il, USA). A p value<0.05 was considered as statistically significant.

Results

Mean age was 59.46±12.93 years in the patient group and 59.00±11.33 years in the control group. The patient and control groups were similar regarding age and gender (Table 1). Age at first attack was 52.00±12.77 years and mean time interval between the first 2 attacks was 6.00±5.52 months. Of the patients, there was obesity in 28 (26.4%), diabetes mellitus in 18 (17.0%), hyperlipidemia in 25 (23.6%), and hypertension in 37 (34.9%). There was family history of gout in 16 patients (15.1%) and tophus in 9 patients (8.5%). Compared to groupII (intercritical period) and the control, no significant difference in MPV levels was found ingroupI (during attack). MPV was similar among the three groups. CRP and ESR were found to be significantly higher in group Ithan in group II and healthy controls (p<0.001 for both). There were significant differences between group I and group II for NLR levels (2.88 vs. 2.19, p < 0.001). NLR levels were also found to be higher in group II compared to healthy controls (p<0.001). When the patients in groupsI and II were stratified according to the presence of tophus, no significant difference was detected in ESR, CRP, MPV, and NLR values (Table 2).

Discussion

In the present study, it was found that NLR values in patients with gout were significantly increased during attack compared to the intercritical period or to the healthy controls, but there was no significant difference in MPV value among groups. The NLR value was significantly higher in patients with gout during the active phase compared to healthy controls. In the current

Table 1. Characteristics of patient and control groups

Characteristic	Gout (n=106)	Control (n=148)	p
Age, years	59.46 ± 12.93	59 ± 11.33	0.246
Male, n (%)	91 (85.8)	128 (86.5)	0.999

Table 2. Parameters evaluated in the groups

Parameter	Group I (during attack period) n=106	Group II (during intercritical period) n=106	Control n=148	p
MPV (f/L)	8.1 (5.9-10.7)	8.2 (5.4-12)	8.3 (6.7-12.9)	0.054
NLR	2.88 (1.21-21.16)	2.19 (0.69-21.82)	1.72 (0.78-11.25)	<0.001†
ESR (mm/h)	36 (24-65)	12.5 (2-30)	-	<0.001
CRP (mg/dL)	35 (19-60)	3.2 (1.6-4.7)	-	<0.001

CRP:C-reactive protein, Normal reference range: 0-10 mg/dL. ESR:erythrocyte sedimentation rate, MPV: mean platelet volume; NLR: neutrophillymphocyte ratio; † There are statistically significant differences in all groups.

literature there is no study evaluating MPV and/or NLR together in patients with gout. This is the first study investigating both MPV and NLR in patients with gout.

MSU crystals are potent inflammatory stimulants which have several mechanisms for interaction with cells. MSU crystals activate cells in the conventional way through opsonization and phagocytosis by cells. These crystals promote stereotypical phagocytic responses such as lysosomal fusion, respiratory burst, and release of inflammatory mediators. In addition, MSU crystals with negative charge interact with lipid membranes and proteins directly but in a non-specific manner through surface characteristics, electrostatic interaction, and hydrogen bonds [3,9].

Symptomatic inflammatory response against urate crystals occurs via both cellular and chemical mediators, including mononuclear cells. MSU crystals bind to Fab of IgG and Fc component reacts with Fc receptors of neutrophils. IgG enhances phagocytosis of crystals and release of superoxide from neutrophils [3,9].

MSU crystals stimulate release of C5a, bradykinin, and kallikrein. Phagocytes enhance production and secretion of many mediators from synovial cells and synovial endothelial cells such as arachidonic acid metabolites, lysosomal proteases, ınterleukin-1 (IL-1), TNF-α, IL-6, reactive oxygen species, collagenase, and adhesion molecule expression (E-selectine). Neutrophil recruitment is induced through activation of endothelium by chemotactic factors, IL-1 and TNF-α. Leukotrien-B4 released from neutrophils, kinin, latent collagenase, kallikrein, prostaglandin-E2 (PGE2), 6-keto PGE1-α,and IL-1alsocontributes to inflammation. Systemic findings such as fever, leukocytosis, and synthesis of acute phase proteins in the liver by IL-1 emerge with TNF-α, IL-6 and IL-8 release into venous circulation [3,9].

Neutrophil apoptosis, inactivation of inflammatory cells, increased anti-inflammatory mediators, coating of MSU crystals with apolipoprotein B and E, and removal of crystals by phagocytosis play an important role in the limitation of acute arthritis over time [3,9].

It has been long known that platelets have important roles in hemostasis. It is known that increased vascular permeability during inflammation and platelets play significant roles in the release of several inflammatory cytokines [10].Platelets change their size and shape when they are activated. Because larger platelets are more active metabolically and enzymatically and involve more granules, platelet functions are correlated to their size [11]. MPV, which represents the average platelet size, is associated with platelet activation. It is reported that increased MPV is associated with Crohn's disease, rheumatoid arthritis, familial Mediterranean fever, ulcerative colitis, acute pancreatitis, ischemic stroke, diabetes mellitus, and myocardial infarction. In recent years, MPV has been considered a simple marker for inflammation in inflammatory disorders [12-17].

In a study on Behcet's disease, the MPV value was found to be significantly higher in the Behcet group compared to controls and it was reported to be associated with predisposition to thrombosis [18].However, in our study, no significant difference was found in MPV value in patients with gout. MPV levels were similar in active and inactive gout disease. When considered according to the presence of tophus, no significant difference was found in the MPV value. In our study, no significant difference was detected in the MPV values of patients with gout during both attacks and intercritical periods compared to healthy controls. Although gout is an inflammatory disease progressing with attacks, lack of thrombotic attacks during the course of disease can explain similar MPV values during attacks compared to intercritical period. Platelets in gout could not be determined as part of inflammatory response.

Neutrophil and lymphocyte counts can be obtained from the leukocyte number in the complete blood count. NLR is considered a marker of inflammation and it is suggested that NLR has prognostic significance in some systemic disorders [7,8,19]. NLR is important as it provides information regarding two different pathways: 1) neutrophils resulting from ongoing inflammation; 2) lymphocytes in the regulatory pathway. In our study, NLR was found to be significantly higher in patients with gout during attacks compared to those in healthy controls and in patients with gout in the intercritical period. The majority of diseases characterized by fever, anemia, and increased acute phase proteins are found to be associated with increased IL-1ß production and bioactivity [20]. In addition, as shown in cryopyrinopathy, there is an anomaly in the signaling pathways of NOD (Nucleotide oligomerization domain)-like receptors in this group of disorders. Inflammasome is a complex formed through stimulation by ligand of one of the NOD-like receptors [21,22]. Inflammasomes are denoted according to the NOD-like receptor that is present in their structure. In this context, three distinct complexes have been described in humans: NACHT leucine-rich repeat and pyrin domain-containing protein 1 (NALP1), NALP3, and Ice protease activating factor (IPAF).To date, NALP3 is the most extensively investigated inflammasome complex. Studies have shown that Toll-like receptor (TLR) and NALP3 inflammasome complex in concert result in IL-1ß and IL-18 production [23]. This becomes a focus of interest in studies on crystal-related arthropathies. It has been shown that monosodium urate and calcium pyrophosphate dihydrate crystals cause activation of NALP3 inflammasome complex by passing into intracellular areas and triggering inflammation in gout and pseudo-gout characterized by accumulation of these substances [21,24].

The finding that NLR was higher in patients with gout in the intercritical period compared to healthy controls can indicate that there is an ongoing inflammatory response during the intercritical period.NLR can be a useful marker for disease activation in patients with gout. Many cytokines and biomarkers have

been investigated as inflammation markers in gout disease [25-30]. However, parameters used in these studies are expensive. NLR is a simple, readily available parameter. In conclusion, we found increased NLR in patients with gout both during attacks and in the intercritical period. This could be important for demonstrating both disease activation and subclinical inflammation. Further studies with larger sample sizes comparing NLR with cytokine levels during the intercritical period will help to elucidate this topic.

Competing interests

The authors declare that they have no competing interests.

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